

# Cavitating pulmonary cryptococcosis developing in an HIV antibody patient despite prior treatment with fluconazole

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## Abstract

**Disseminated cryptococcosis developed in an HIV antibody positive patient who was taking fluconazole for oral candidiasis. This case highlights the poor response to therapy that may be seen, and the severe pulmonary complications that may ensue. The use of fluconazole prior to the development of cryptococcosis did not confer protection.**

## Introduction

*Cryptococcus neoformans* is a rare but significant cause of pneumonia in patients infected with the human immunodeficiency virus (HIV). The spectrum of disease caused by the fungus varies considerably from asymptomatic pulmonary cryptococcosis to widespread disseminated disease including, commonly, meningitis.<sup>12</sup> The drug of choice in the treatment of this disease is amphotericin B, but recently interest has focused on the role of the azoles, particularly fluconazole.

## Case report

Four weeks prior to admission with headache, a 37 year old West Indian heterosexual was found to be HIV antibody positive after he presented with oral candidiasis. Serum cryptococcal antigen at this time was negative. He was started on fluconazole (50 mg/day).

On examination, at admission, he was pyrexial (38°C) with mild neck stiffness. A chest radiograph revealed soft shadowing in the left upper zone. Examination of the cerebrospinal fluid (CSF) showed budding yeast on India ink stain which was subsequently cultured and identified as *Cryptococcus neoformans* var. *neoformans*. Blood cultures and sputum cultures also grew *C neoformans*. The MIC to fluconazole of *C neoformans* isolated from the CSF sample was 25 mg/ml. He was hyponatraemic.

He was treated with amphotericin B (0.6 mg/kg/day) for three weeks but developed renal impairment (creatinine clearance falling to 28 ml/minute) and subsequently fluconazole (400 mg/day), and flucytosine (100 mg/kg/day) but he deteriorated and developed leucopenia (WBC count  $0.7 \times 10^9/l$ ). Further chest radiographs (fig 1) and CT (fig 2) showed increasing consolidation with cavitation and scattered intrapulmonary nodules. Bronchoscopic examination

with bronchoalveolar lavage confirmed pulmonary cryptococcosis. He was treated for a further month with liposomal amphotericin B (3 mg/kg/day) but continued to deteriorate and died two months after admission.

Postmortem examination revealed widespread involvement in both lungs by *C neoformans*. No other pathogens were detected.

## Discussion

Cryptococcal infection occurs in 5–10%<sup>1-7</sup> of all patients with the acquired immunodeficiency syndrome (AIDS) and is the fourth most common infection found in AIDS patients after *Pneumocystis carinii*, cytomegalovirus, and mycobacterial infections.<sup>8</sup> Cryptococcosis is the initial manifestation of AIDS in 40% to 45% of such patients.<sup>1</sup>

The lung is the usual site of entry of *C neoformans* and of those infected 50% to 80% are immunocompromised.<sup>9</sup> Cryptococcal infection may be limited to the lungs in immunocompetent hosts, whereas disseminated disease and meningitis<sup>10</sup> are more common in immunocompromised hosts. Pulmonary cryptococcosis is probably more common

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Accepted for publication  
22 October 1991

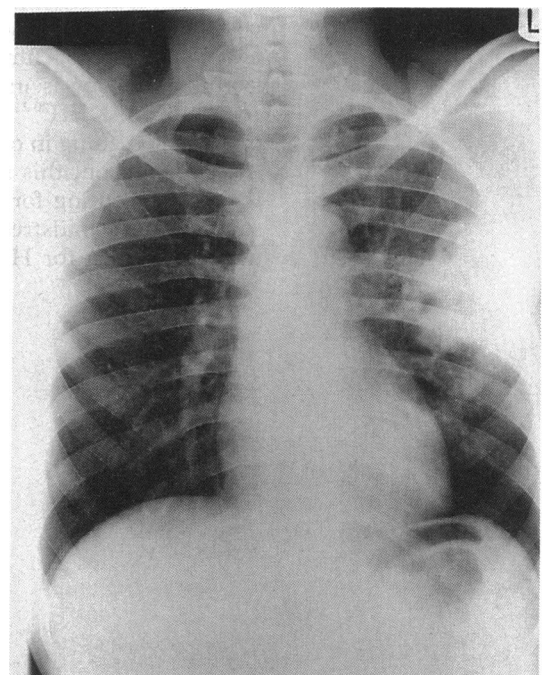
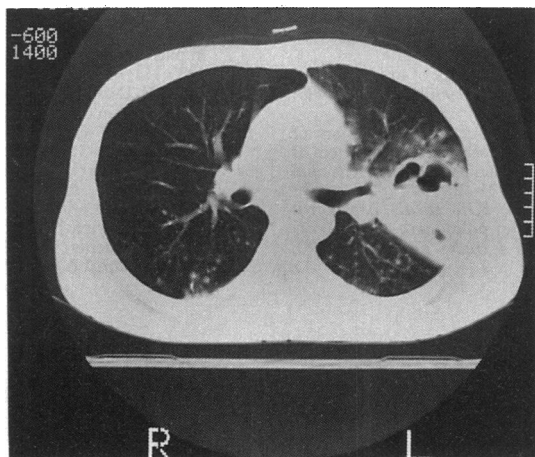


Fig 1 Chest radiograph 6 weeks after admission showing involvement of both lung fields and cavitation in the left lung.

Fig 2 CT scan of the thorax at 6 weeks showing cavitation in the left lung.



than has been previously realised; Cameron *et al*<sup>2</sup> reported an incidence of 39% in AIDS patients with cryptococcosis and Zuger *et al* found that 6 of 22 (27%) patients who presented with cryptococcal meningitis had pulmonary involvement.<sup>3</sup> Cavitation is, however, unusual.<sup>9,11,12</sup> It appears to be commoner in immunocompromised patients. In 15 patients studied by Khoury *et al*<sup>9</sup> who were immunocompromised owing to corticosteroid therapy, malignancy, alcoholism, or post-operative status, the presentation varied widely from solitary or multiple pulmonary nodules, with and without cavitation, to patchy infiltration, pleural effusion, or adenopathy. Of the nine immunocompetent patients studied none developed cavitation and lung involvement was less extensive. However, in contrast, none of the seven AIDS patients studied by Miller *et al*<sup>13</sup> had large nodules, cavitation, or alveolar infiltration and none of the 12 AIDS patients in the review by Cameron *et al*<sup>2</sup> had evidence of cavitation.

T-cell-dependent responses are the primary factors responsible for recovery from cryptococcal infection,<sup>14</sup> thus explaining the poor outlook in AIDS patients. The inability of the host to mount an inflammatory response necessary to make a nodule or infiltrate radiographically apparent has been suggested in AIDS, in contrast to other immunocompromised patients without AIDS.<sup>13</sup> The case described here shows the unusual development of widespread nodules and cavitation in the context of AIDS. The more pronounced radiographic features may have resulted from less marked immunosuppression in this case though immunological markers are unfortunately unavailable. Alternatively prior treatment with fluconazole may have altered the natural progression of the disease.

Fluconazole is effective in the treatment of oral candidiasis, and has been used with success in the treatment of cryptococcosis.<sup>15</sup> It is a selective inhibitor of fungal cytochrome P450 which is necessary for the synthesis of ergosterol,<sup>16</sup> the essential sterol in fungal membrane. Amphotericin B binds to ergosterol causing increased cell permeability and cell death. Though hyponatraemia and positive cultures for cryptococci from

extrameningeal sources, as seen in this patient, indicate a poor prognosis,<sup>1</sup> prior therapy with fluconazole may have reduced ergosterol levels and therefore have prevented full benefit from amphotericin B. Alternatively, use of fluconazole prior to the development of cryptococcosis may have selected an isolate with a high MIC to fluconazole and poor response to the higher dose subsequently given. However, the laboratory sensitivity of azole antifungal drugs is highly dependent on test conditions,<sup>17</sup> and MICs for responsive strains that are higher than the concentration of the drug attained in the responsive patient may be seen.

Liposomal amphotericin B (AmBisome) has been used with success in the treatment of cryptococcal meningitis,<sup>18</sup> pulmonary aspergillosis,<sup>19</sup> and other systemic fungal infections.<sup>20</sup> It appears to be less nephrotoxic than conventional amphotericin B, hence its use here, though its efficacy is still unknown. Results of clinical trials are awaited. Flucytosine may be effective but is limited by its considerable toxicity profile,<sup>1,6,21,22</sup> as was the experience in this case. The current dosage recommendation of 150 mg/kg/day may be too high and 75–100 mg/kg/day is perhaps adequate.<sup>23</sup>

Awareness that cryptococcal infections may occur despite patients already taking systemic antifungal drugs is important. Further studies are required to establish possible interactions between the azoles and amphotericin B. Though unusual, cavitation may be a feature of pulmonary cryptococcosis in AIDS.

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